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**A case of ruptured HCC in resolving NASH associated with type  
2 diabetes: Is early detection of diabetes-related HCC feasible?**

*Running title: Ruptured HCC in resolving NASH*

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At present, one of the most critical problems for patients with type 2 diabetes mellitus (T2DM) is digestive organ cancers which are now considered a major cause of death. The risk of hepatocellular carcinoma (HCC), in particular, is approximately four times greater in diabetics compared to non-diabetic individuals.<sup>1</sup> Nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH), appears to play a significant role in T2DM-related hepatocarcinogenesis, but the detailed underlying pathological mechanism remains to be clarified.<sup>2</sup> One would assume that individuals with T2DM and NAFLD should at least be closely followed up as high-risk patients. But, is this sufficient as a strategy in the care of T2DM patients?

Recently we encountered a case of a ruptured HCC associated with T2DM. We report herein the case, to alert and activate discussion about current and future strategies for T2DM-related HCC. A 52-year-old man was urgently admitted to our hospital because of intra-abdominal hemorrhage. Imaging detected a 50mm tumor in the right lobe of the liver (Fig. 1A), and a clinical diagnosis of a ruptured HCC was made. Embolization was immediately performed and controlled the bleeding successfully.

In the previous 2 years, the patient had been treated for T2DM and hypertension with metformin, linagliptin and amlodipine. His body mass index was 24kg/m<sup>2</sup> and waist circumference was 84cm. He was not a habitual drinker. Serum markers of hepatitis viruses and autoantibodies were negative, liver function tests had never been abnormal, and he had no history of chronic liver disease or tumor (Fig. 1B).

Three weeks after admission, the liver tumor was surgically removed (Fig. 1C). Histological examination showed complete coagulative necrosis (Fig. 1D), but the tumor could still be recognized as HCC (Fig. 1E). The background liver was non-cirrhotic and had steatosis in <5% hepatocytes (Fig. 1F), minimal acinar

inflammation, and rare typical ballooned hepatocytes (Fig. 1H) containing Mallory-Denk bodies (MDB) (Fig. 1I). There was only zone 3 sinusoidal fibrosis (Fig. 1G). Based on the currently accepted NAFLD/NASH histological criteria,<sup>3,4</sup> a diagnosis of steatohepatitis could not be made because of the absence of “significant” steatosis. However, the additional presence of hepatocyte ballooning with MDB and typical zone 3 sinusoidal fibrosis supported our final clinicopathological diagnosis of HCC associated with “resolving NASH”. The antidiabetic drugs might have alleviated steatosis and disease activity, and the overall histological picture in the background liver represented NASH resolution.<sup>5</sup>

Presence of fat droplets in 5% of hepatocytes is currently approved as the threshold for the histological diagnosis of pathological fat accumulation in liver tissue,<sup>3,4</sup> and is possibly the lowest level detectable with modern imaging devices. However, strictly adhering to this criterion for diagnosing steatosis entails the risk of missing the diagnosis of NAFLD/NASH and related complications. It is important to recognize that diabetes-related “NAFLD/NASH”, especially in treated patients, may present with a non-pathologic level (<5%) of steatosis and that HCC can develop asymptotically, like a silent killer, in non-cirrhotic liver. Eventually, all diabetic patients need close follow-up with regular imaging examinations to possibly detect T2DM-related HCCs at an early stage.

## Disclosure

The authors have no conflicts of interest to declare.

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## Figure legends

Figure 1 The patient's present and past radiological findings (**A,B**) and pathologic findings from the resected liver (**C-I**). (**A**) Magnetic resonance image (T2 weighted) on admission. A round tumor with a mosaic internal structure (ø50 mm; arrow) is evident in the right hepatic lobe. (**B**) Computed tomography (plain) 15 months before admission. No specific findings, including tumor or steatosis, can be detected. (**C**) Cut-surface of the specimen. A brown, well-circumscribed tumor (ø50 mm) is shown. (**D,E**) Histologically, the tumor was necrotic but still recognizable as HCC (**D**, Hematoxylin-eosin stain, original magnification x280; **E**, Immunostain for HepPar1, original magnification x400). (**F,G**) Background liver tissue shows minimal steatosis, mild acinar inflammation, and zone 3 sinusoidal fibrosis (**F**, Hematoxylin-eosin stain, original magnification x60; **G**, Azan-Mallory stain, original magnification x60). (**H,I**) Rare presence of ballooned hepatocytes (**H**, Hematoxylin-eosin stain, original magnification x400) and MDB in the non-neoplastic liver (**I**, Immunostain for p62, original magnification x400).

